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EUROPEAN PATENT APPLICATION

⑲ Application number: **89110402.8**

⑤① Int. Cl.4: **A61K 9/18 , A61K 9/50**

⑳ Date of filing: **08.06.89**

Claims for the following Contracting States: ES
+ GR.

③① Priority: **09.06.88 US 204437**

④③ Date of publication of application:
13.12.89 Bulletin 89/50

⑥④ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

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⑤④ **Drug in combination with flavor masking agent and method for making same.**

⑤⑦ According to this invention various hygroscopic malflavored drugs can be proceeded by a unique wet granulated process wherein a slurry of the drug in water is dried in combination with colloidal silicon dioxide and, in a particularly preferred embodiment microcrystalline cellulose with the colloidal silicon dioxide absorbing onto the drug particles.

The result is a protective coating of silicon dioxide which masks unpleasant taste and odor and also reduces the adhesive of the granulation onto the punch faces used in the manufacture of the granules. By adsorbing silicon dioxide on the particulate surface of the malflavored hygroscopic drug, the drug becomes not only easier to handle but the unpleasant tastes and/or odors are masked making the final product more susceptible to proper patient compliance.

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DRUG IN COMBINATION WITH FLAVOR MASKING AGENT AND METHOD FOR MAKING SAME

Drugs are most commonly administered orally and as such must be placed in a suitable form for oral ingestion. Not only must the drug be adapted to be delivered at desirable dosage levels but, at times, depending upon the nature of the drug, must be protected from rapid moisture absorption.

Certain hygroscopic drugs have distinctly unpleasant tastes and odors. In addition hygroscopic and waxy drugs present processing problems during tabletting and encapsulation. Examples of drugs which possess one or more of these properties are oxtriphylline, procainamide HCl, gemfibrozil, disopyramide phosphate, fenoprofen calcium, atenolol, piracetam, carbamazepine, tetracycline HCl, oxytetracycline HCl, rifampin, lincomycin HCl, clindamycin HCl, cefaclor, cefadroxil, cephradine, thiamine HCl, ascorbic acid, acetylsalicylic acid, methocarbamol, methyl dopa, sulindac, desipramine HCl, ranitidine HCl, ethionamide, divalproex sodium, meprobamate, captopril, and aminophylline. These drugs as well as other hygroscopic unpleasant tasting drugs are known for purposes of this specification as malflavored drugs and, because of their off flavors and difficult handling, provide problems both for the drug manufacturer as well as in the area of patient compliance in taking proper amounts.

Silicon dioxide is an ingredient commonly used in the tablet art as an aid to tablet processing. Low levels of silicon dioxide usually below 2% are generally employed. European Patent Application 108,218 by James Michael Dunn et al describes the formation of constant release rate tablets of water soluble drugs employing from 0.5 to 3 rate percent of fumed silicon dioxide as a lubricant.

U.S. Patent 4,536,511 issued to Wolfgang Fisher et al, discloses a drug specific combination including levels of silica and cellulose below 1% evidently to aid binding and flow characteristics in a wet granulation system for the drug muzolimine.

U.S. Patent 4,526,777 issued to Cheryl D. Blume et al disclosed the combination of two dry granulations including microcrystalline cellulose as a binding and disintegrant with syloid as a flow enhancer again in preceding low levels.

Patents issued to James M. Dunn, namely U.S. 4,461,759; 4,522,804; 4,521,402; and 4,521,401 disclose 0.4 to 3.09 % silicon dioxide in combination with hydrogenated vegetable oil and an acrylic acid polymer.

U.S. Patent 4,609,675 issued to Robert M. Franz discloses using silicon dioxide at a 1% level for dry granulation of ibuprofen.

U.S. Patent 4,478,819 issued to Hercelin, teaches silicon dioxide used in forming extruded granules. U.S. Patent 4,442,086 issued to James M. Quinlan discloses the use of silica as a glidant at levels not greater than 0.05%.

U.S. Patent 4,415,547 teaches the use of silica dioxide as a dusting powder for pellets which are subsequently compressed into tablets.

U.S. Patent 3,592,927 issued to Maximilian Koffier discloses a calcium pantothenate composition which is produced in dry free flowing form by the inclusion of silicon dioxide during its manufacture at a level below 5%.

In addition, European Patent Application 167,191 discloses the inclusion of silicon dioxide as an aid to direct compression of tablets. European Patent Application 136,100 discloses the combination of sucralose with microcrystalline cellulose and colloidal silicon dioxide as a suspending agent at extremely low levels.

Summary of the Invention

According to this invention various unpleasant flavored drugs can be processed by a unique wet granulation process wherein a slurry of the drug in water is dried in combination with colloidal silicon dioxide and, in a particularly preferred embodiment microcrystalline cellulose is used with the colloidal silicon dioxide adsorbing onto the drug particles.

By unpleasant flavored drugs, for purposes of this invention, the term is defined as drugs which are unpleasant tasting and/or smelling and/or are hygroscopic and/or tacky.

The result is a protective coating of silicon dioxide which masks unpleasant taste and odor, decreases moisture absorption, and also reduces the adhesiveness of the granulation onto the punch faces used in the manufacture of the granules. By adsorbing silicon dioxide on the particulate surface of the malflavored hygroscopic drug, the drug becomes not only easier to handle but the unpleasant tastes and/or odors are masked making the final product more susceptible to proper patient compliance.

Detailed Description of the Invention

Levels of silicon dioxide generally greater than 3% by weight of the combination of the drug and the other solid components are necessary to provide a noticeable masked effect and in fact levels of between 4 and 15% of silicon dioxide are particularly preferred although, with certain particularly unpleasant drugs levels of silicon dioxide approaching 30% can be utilized within the teachings of this invention.

The drug used in the combination is usually present at a level of 30 to 70% by weight with other commonly used granulating and tableting aids being added as necessary or desired as within the skill of the art to provide a total dry weight combination of 100%.

Particularly preferred is the addition of a drying adjunct with microcrystalline cellulose being especially preferred at levels up to about 45% by weight of the combination. Microcrystalline cellulose also serves as a filler-binder which helps form particularly suitable granules and aids in the compression of the granules during tableting.

As mentioned above, this invention involves a unique wet granulation process wherein colloidal silicon dioxide and preferably other excipients, especially microcrystalline cellulose are adsorbed onto particles of a particular hygroscopic malflavored drug. Once the granulation process is completed the mixture is dried in an oven, milled and tabletted to an appropriate sized tablet. Lubricants and disintegrants may be added to the formulation prior to tableting as well as suitable coloring agents as is well known in the art. Tablets with excellent compressibility and over 20 kg hardness may be achieved at relatively low tableting forces. The same process is useful for preparing granules to be placed in hard gelatin capsules.

In addition, film coating can be used to provide an additional moisture barrier.

Drugs which particularly benefit from the process of this invention are 3-phenoxy pyridine monosulfate pramiracetam, and gemfibrozil. When these drugs are used in combination with from 3 to 20% and particularly 5 to 20% of silicon dioxide the difficulties inherent in their manufacture are substantially diminished and the malflavor of these drugs is also minimized. (Pramiracetam is (N-[2-Bis(1-methylethyl)-amino]ethyl]-2-oxo-1-pyrrolidine acetamide, sulfate (1:1)).

Examples of the process of this invention follow with two specific drugs used. It is to be understood that the examples are merely illustrative of malflavor drugs. The ingredients used in the first example are set forth in the table below.

EXAMPLE 1

TABLE I

Ingredients	Per 1000
TABLET CORE	
3 phenoxy pyridine monosulfate	786.450 g
Colloidal Silicon Dioxide NF	2.359 g
Water, Purified	120.000 ml
Sodium Lauryl Sulfate NF	2.280 g
Crospovidone NF	22.800 g
Colloidal Silicon Dioxide NF	177.911 g
Microcrystalline Cellulose NF Powder	91.200 g
Crospovidone NF	34.200 g
Calcium Stearate NF, Powder	11.400 g
Talc USP	11.400 g
Water, Purified	q.s.
	1140.00 g

A sample was prepared as indicated by first milling the drug with colloidal silicon dioxide through a 1B screen utilizing a hammer mill. Separately, sodium lauryl sulfate is added to water in a planetary mixer and then the aqueous mixture is mixed with the combination of silicon dioxide and 3 phenoxy pyridine monosulfate. Crospovidone is then added to aid in disintegration.

Colloidal silicon dioxide is then added and mixed for about 5 minutes followed by the addition of microcrystalline cellulose. The granulation is then dried in an oven at 50 °C to a moisture content of less than 0.5% and further processed by milling through a 18 screen and then combined with calcium stearate, crospovidone and talc. Tablets are formed by compressing 1140 mg of the mixture to a hardness generally

The tablet is then film coated with a mixture of about 4% coat containing hydroxypropylmethylcellulose.

EXAMPLE 2

TABLET CORE	
Pramiracetam (salt equivalent)	544.200 g
Water, Purified	95.000 ml
Colloidal Silicon Dioxide NF	50.000 g
Microcrystalline Cellulose NF	328.880 g
Crospovidone NF	61.200 g
Calcium Stearate NF, Powder	25.500 g
Talc USP	10.200 g
	<u>1020.000 g</u>

The drug in accordance with this invention is made as follows: first the pramiracetam was dissolved in water in a planetary type mixer and then colloidal silicon was added and mixed for about 5 minutes to partially dry the slurry. Subsequently microcrystalline cellulose was added and mixing continued for approximately 5 minutes. The granulation was then dried at 35 °C for 6 hours and dried subsequently at 50 °C to a moisture content of less than 1%. The granulation was then milled through a 18 screen with knives forward at medium speed and calcium stearate was then added to the screen with a subsequent addition of crospovidone and talc. The mixture was blended for five minutes and the tablets were then compressed to a weight of 1020 mg and a hardness of 14 to 16 kilograms using an elliptical punch.

It is apparent that with the teachings of this invention apply to a variety of other drugs having malflavors.

Claims

1. In combination, a particulate unpleasant flavored drug and at least 3% by weight of the combination of SiO₂ adsorbed on said drug particle, SiO₂ being present at a level sufficient to minimize the unpleasant flavor effects of the drug.

2. The combination of Claim 1 wherein the SiO₂ is present at a level of not more than 30% by weight of the combination.

3. The combination of Claim 1 wherein SiO₂ is present at a level of 4-15% by weight of the combination.

4. The combination of claims 1, 2 or 3 wherein the drug is present at a level of 30 to 70% by weight of the combination.

5. The combination of claim 1 wherein an adjunct is added to further dry the formulation.

6. The combination of claim 5 wherein the adjunct is microcrystalline cellulose.

7. A tablet formed from the combination of claim 1, 2, 3, 5 or 6 comprising at least one member selected from the group consisting of excipients, disintegrants and glidants.

8. A process for the production of a solid malflavored drug dosage form wherein the malflavor is substantially minimized comprising:

a) forming a slurry of the drug in water

b) adsorbing colloidal SiO₂ on the surface of the drug to form a protective flavor masking coating;

and

c) drying the combination.

9. The process of claim 8 wherein microcrystalline cellulose is added with the SiO₂.

10. The process of claim 8 wherein examples are milled and tabletted.
11. 3-phenoxy pyridine monosulfate in combination with SiO₂ at a level of between 3 and 20% by weight of the combination.
12. Pramiracetam in combination with SiO₂ at a level of between about 3 and 20% by weight of the combination.
13. Gemfibrozil in combination with SiO₂ at a level between about 3 and 20% by weight of the combination.
14. The combination of claims 11, 12, or 13 wherein microcrystalline cellulose is present at a level of about 5-45% by weight of the combination.

Claims for the following Contracting States: ES, GR

1. A process for the production of a solid malflavored drug dosage form wherein the malflavor is substantially minimized comprising:
 - a) forming a slurry of the drug in water
 - b) adsorbing colloidal SiO₂ on the surface of the drug to form a protective flavor masking coating; and
 - c) drying the combination.
2. A process according to claim 1, wherein the SiO₂ is added in an amount of not more than 30% by weight of the combination.
3. A process according to claims 1 and 2, wherein the SiO₂ is added at a level of 4 to 15% by weight of the combination.
4. A process according to claims 1 to 3, wherein the drug is present at a level of 30 to 70% by weight of the combination.
5. A process of claims 1 to 4 wherein an adjunct is added to further dry the formulation.
6. A process of claim 5 wherein the adjunct is microcrystalline cellulose.
7. A process according to claims 1 to 6 wherein at least one member selected from the group consisting of excipients, disintegrants and glidants is added.
8. The process of claim 6 wherein microcrystalline cellulose is added with the SiO₂.
9. The process of claims 1 to 8 wherein examples are milled and tabletted.
10. The process of claims 1 to 9 wherein 3-phenoxy pyridine monosulfate is added in combination with SiO₂ at a level of between 3 and 20% by weight of the combination.
11. The process of claims 1 to 9 wherein pramiracetam is added in combination with SiO₂ at a level of between about 3 and 20% by weight of the combination.
12. The process of claims 1 to 9 wherein gemfibrozil is added in combination with SiO₂ at a level between about 3 and 20% by weight of the combination.
13. The process of claims 10, 11, or 12 wherein microcrystalline cellulose is added at a level of about 5-45% by weight of the combination.

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30 Priority: **09.06.88 US 204437**

43 Date of publication of application:
13.12.89 Bulletin 89/50

64 Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

68 Date of deferred publication of the search report:
11.04.90 Bulletin 90/15

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	EP-A-0 219 458 (WARNER-LAMBERT CO.) * Page 2, line 8 - page 4, line 1, page 8, lines 1-17; example 5,1; page 5, line 28 - page 6, line 23 *	1,3-7, 11-14	A 61 K 9/18 A 61 K 9/50
Y	---	9	
X	US-A-4 338 311 (R.A. HEASLEY) * Column 1, lines 15-28, line 53 - column 2, line 35 *	1,2,4,8 ,10	
Y	---	9	
D,X	US-A-3 592 921 (M. KOFFLER et al.) * Column 1, line 67 - column 2, line 8, lines 31-65 *	1-3	
D,Y	---	1-4,7	
Y	US-A-4 486 435 (SCHMIDT et al.) * Column 1, line 64 - column 2, line 19, column 3, line 38 - column 4, line 65 *	1-4,7	
X	-----	8,10	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 15-01-1989	Examiner SITCH W.D.C.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document			